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(21) International Application Number: PCT/IB99/01735 (22) International Filing Date: 26 October 1999 (26.10.99) (30) Priority Data: 454/DEL/99 19 March 1999 (19.03.99) IN (71) Applicant (for all designated States except US): RANBAXY LABORATORIES LIMITED [IN/IN]; 19, Nehru Place, New Delhi 110 019 (IN). (72) Inventors; and (75) Inventors/Applicants (for US only): MUKHERJI, Gour [IN/IN]; E-12/31, Phase - 1, DLF Qutab Enclave, Gurgaon - 122 002, Haryana (IN). KUMAR, Manoj [IN/IN]; House No. 157, Sector - 16A, Faridabad 121 001, Haryana (IN). SEN, Himadri [IN/IN]; S-1/19, Phase - III, DLF Qutab Enclave, Gurgaon 122 002, Haryana (IN).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: TASTE MASKING COATING COMPOSITIONS (57) Abstract A coating composition is described for the film coating of pharmaceutical cores containing the drug, said composition comprising a suitable film forming material in combination with a high viscosity swellable polymer.		

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TASTE MASKING COATING COMPOSITIONS

FIELD OF THE INVENTION

The present invention relates to a coating composition effective for taste masking of bitter and unpalatable drugs.

BACKGROUND OF THE INVENTION

Most prescription and non-prescription drugs are administered orally as tablets or capsules. However, patients at the extremes of age, such as children and the elderly, often experience difficulty in swallowing such solid dosage forms. For such patients drugs can be provided either as chewable or dispersible tablets or, as liquid dosage forms such as solutions, emulsions and suspensions. These dosage forms permit perceptible exposure of the active drug to the taste buds. Some drugs are extremely bitter and therefore unpalatable when given in these dosage forms. As a consequence, measures need to be taken to mask the taste of these drugs in order to enhance patient compliance.

Several techniques to make liquid dosage forms palatable, are reported in the literature. These include the use of relatively insoluble salts of the parent drug resulting in lower exposure of the drug in perceptible form in the mouth. Syrups with or without flavouring, are often sufficient to mask the taste of drugs. However, some drugs have such a pronounced bitterness that conventional approaches such as the use of sweeteners, amino acids, flavors and adsorbents are unsuccessful. This is particularly problematic if the drug in question is extensively used in treating children or the elderly. There is, therefore, a need to develop approaches that would be effective in masking the taste of bitter drugs.

US 4,808,411 describes a taste masked pharmaceutical composition comprising erythromycin or its derivatives and a carbomer. The drug-polymer complex is believed to be held together by ionic attraction between the amine group of erythromycin compound and carbonyl group of the carbomer, and by the gel properties of the insoluble carbomer. This provides for a minimal dissolution of the erythromycin compound in a non-ionic aqueous medium, so that the drug is released from the complex slowly enough to avoid a significant perception of bitterness in the mouth. In the gastro-intestinal tract, the ionic environment causes liberation of the erythromycin compound. Thus, by controlling the availability of the drug in the free form, taste masking of the drug is achieved. This method, however, will be useful for masking the taste of only those drugs which can form reversible complexes and will, therefore, be limited in its utility.

US 4,865,851 describes a taste masked formulation of cefuroxime axetil where the drug particles are provided with integral coatings of a lipid or mixtures of lipids which are insoluble in water and which serve to mask the bitter taste of cefuroxime axetil upon oral administration. This coating however, results in a significant reduction in the dissolution and consequently the bioavailability of cefuroxime axetil suspension is significantly low as compared to tablet dosage form.

US 5,695,784 describes a method for taste masking of bitter drugs where the coating composition comprises a cationic copolymer of dimethylaminoethyl methacrylate and neutral methacrylate acid esters, neutral methyl esters and/or ethyl ester compounds of polymethacrylic acid, quaternary ammonium compounds of

polymethacrylic acid or ethylcellulose and triethylcitrate and optionally hydroxypropyl methylcellulose. This coating composition requires the application of large quantities of polymers for effective taste masking.

SUMMARY OF THE INVENTION

The present invention describes coating compositions and processes for the preparation of a pharmaceutical coating composition, effective in masking the taste of medicinal compounds, to be applied over the core constituted of medicinal compound. The core may comprise primary drug particles, granules, crystals, pellets or even unit dosage forms like tablets. The coat comprises a film forming polymer and a high viscosity swellable polymer, optionally also including other suitable ingredients for coating including lubricants, plasticizers and channeling agents.

The combination of film forming polymer with swellable polymer imparts in the film a barrier property for the control of initial drug release suitable for taste-masking, without compromising on drug release over the stipulated duration of a conventional, immediate release formulation. For very bitter drugs polymer applications may be as high as 80% on fine cores using conventional coating polymers. The present composition is capable of achieving the same degree of taste masking in as little as 10 to 15% of polymer application, equivalent to 20 - 30% of total solids applied. This, therefore, results in uniformity of coating thickness, process reproducibility, faster rate of dissolution and uncompromised bioavailability. It also makes the process cost effective and less time consuming.

A variety of polymeric materials can be employed for film forming. Non-limiting examples of such film forming polymers may belong to the class of acrylic polymers, cellulosic polymers or vinyl polymers. The acrylic polymers used will be those available under the trade name Eudragit® from Rohm Pharma. More preferably the acrylic polymers may be methacrylic acid co-polymers sold under the trade name Eudragit L® and Eudragit S®, and polyethylacrylate-methylmethacrylate sold under the trade name, Eudragit NE®.

Cellulosic film-forming agents which are useful, include, alkylcelluloses, such as, methyl or ethyl cellulose and, hydroxyalkylcelluloses (eg., hydroxypropylcellulose or hydroxypropylmethyl-celluloses). The alkyl cellulosic film forming polymers include those sold under the trade names Methocel E™ and Surelease by Dow Chemicals, and Aquacoat® of FMC. Examples of vinyl film forming polymers include polyvinyl acetate or polyvinyl acetate phthalate. The dry weight of the film forming polymer may be applied to a maximum of 30% of the weight of the core for taste masking.

The swellable polymers which may be used in combination with the film forming polymers include carbopol, high viscosity gums, carrageenan, high viscosity vinyl polymers or high viscosity cellulosic polymers such as Methocel™ K series polymers (Trademark Dow Chemicals). Swellable polymers may be present from 0.1 - 20% of the dry weight of film forming polymer.

The coating composition may optionally include pharmaceutically acceptable excipients, which are conventionally used as a channeling agent such as starch, lactose or (PEG) poly ethylene glycol. The channeling agent may be present upto

100%, preferably 60%, or more preferably, upto 30% of the dry weight of the film forming polymer.

The coating composition also contains lubricants which function as anti-sticking agents (e.g. talc, colloidal silica and magnesium stearate) and pharmaceutically acceptable plasticisers (e.g. triethyl citrate, polyethylene glycol, glyceryl monostearate, glyceryl triacetate, acetyl triethylcitrate, triethylcitrate, dibutyl phthalate and dibutyl sebacate). The lubricant quantity may be upto 200% of the dry weight of film-forming polymer, and more preferably, upto 100% of the dry weight of the film-forming polymer. The plasticiser quantity may be upto 40% the dry weight of the film forming polymer. The coated formulations may optionally be cured at elevated temperatures.

A total polymer content in the coating of upto 30% by weight of pharmaceutical cores or, more preferably, 10% by weight of pharmaceutical cores is sufficient to mask the taste of bitter tasting, highly water soluble drugs.

The taste masked coated particles obtained by the composition of the present invention, can be mixed with food or beverages, can be used to prepare liquid suspensions for oral administration, or can be formulated into conventional whole, chewable, or dispersible tablets for oral administration. In forming tablets or liquid suspensions, pharmaceutically acceptable ingredients well known in conventional arts can be employed. For use in suspensions, a mean average particle size of less than 50 mesh (297 microns) is preferred. The drug may optionally be first formulated as pellets, tablets or capsules, which may then be coated for taste-masking.

The examples given herein further illustrate the invention and are not intended to limit the scope of the invention:

DETAILED DESCRIPTION OF THE INVENTION

EXAMPLE 1

Table 1.1 shows a coating composition which has been used for taste masking of a number of drug cores :

Table 1.1

Ingredient	Amount used (g)	Dry wt. (g)
Eudragit L30D	333.33	100.0
Carbomer (Aqueous Carbopol® 971P Dispersion 1% w/w)	200.0	2.0
Talc USP (Aqueous Talc Dispersion 30% w/w)	40.80	102.0
Polyethylene glycol USNF (PEG 1500)	15.3	15.3
Purified Water USP upto..	1000.00	-

To prepare the coating solution, an aqueous talc dispersion (30% w/w), was added to a 1% w/w carbopol dispersion in water under stirring for 30 minutes.

Carbopol-talc dispersion was finally added into plasticized (with PEG 1500) Eudragit dispersion with stirring for 30-40 minutes.

Procedure for preparation of core particles :

Table 1.2

Ingredient	Amount used (g)
Norfloxacin USP	260.0
Microcrystalline Cellulose USNF (Avicel® PH 102)	88.0
Pregelatinized Starch USNF (Sarch 1500)	10.0
Povidone USP (PVP K-30)	30.0
Colloidal Silicon Dioxide USNF (Aerosil® 200)	2.0
Magnesium Stearate USNF	0.75

Weighed amount of ingredients (except Aerosil 200) were sifted through British Standard Sieve (BSS) #44 and mixed for 10 minutes in a double cone blender, followed by the addition of Aerosil 200 (sifted through BSS #60) and an additional mixing of 2 minutes. The blend was then granulated with water and dried at 60°C in a tray-drier for 24 hours. The granules obtained were sifted to give (BSS)# 44 / #85 fraction.

Resultant granules (150g) were lubricated with 0.5% magnesium stearate and sprayed with the prepared coating solution using Wurster coater (Glatt GPCG-1 from Glatt GmbH, Germany). The total polymer content of the applied coat was 12.0% by weight of the core while the total solids applied was 26% by weight of the core. A total polymer coating of only 12% was sufficient to mask the bitter taste of Norfloxacin while giving optimum dissolution required for immediate release formulations. (Table 1.3).

Table 1.3

Time (Min.)	Percent drug released	
	USP Buffer pH 4.0; 50rpm; 900ml	
	Uncoated	Coated
5	63.80	2.30
10	95.73	19.40
15	106.40	38.30
20	--	54.23
25	--	66.37
30	--	82.17

EXAMPLE 2

In this example, ibuprofen was granulated and coated for taste masking, as discussed below.

Table 2.1

Ingredient	Amount used (g)
Ibuprofen USP	260.0
Microcrystalline Cellulose (Avicel® PH 102)	88.0
Pregelatinized Starch USNF (Starch 1500)	10.0
Povidone USP (PVP K-30)	30.0
Colloidal Silicon Dioxide USNF (Aerosil® 200)	2.0
Magnesium Stearate USNF	0.75

Weighed amounts of Ibuprofen, Avicel 102, Starch 1500 and PVP K-30 were sifted through BSS #44 and mixed for 10 mins. in a double cone blender. Aerosil 200 was sifted through BSS #60 and added to the blend in the double cone blender and mixed for an additional 2 minutes. The blend was granulated with water and dried at 60°C in a tray drier for 4 hours. After sifting through BSS #44 and BSS #85, the #44/85 fraction (150gm) was lubricated with magnesium stearate (0.75g). The dried and lubricated granules (150.0g) were sprayed with the prepared coating solution as described in Example 1 (Table 1.1). Only a 6% coating of polymers by weight of the core (total solids applied was 13%) was sufficient to mask the taste of ibuprofen. Coated granules when kept in the mouth for 1-2 minutes, did not give any bitter taste. The dissolution of ibuprofen was not significantly affected by this coat, as shown in the Table 2.2.

Table 2.2

Time (Min.)	Percent drug released	
	Phosphate Buffer pH 7.2; 150rpm; 900ml	
	Uncoated	Coated
5	54.30	46.27
10	85.63	76.03
15	94.06	88.97
20	97.00	93.37
25	97.40	93.00
30	97.90	94.70

EXAMPLE 3

Table 3.1

Ingredient	Amount used (g)
Etodolac BP	200.0
Microcrystalline Cellulose USNF (Avicel® PH 102)	148.0
Pregelatinized Starch USNF (Starch 1500)	10.0
Povidone USP (PVP K-30)	30.0
Colloidal Silicon Dioxide USNF (Aerosil® 200)	2.0
Magnesium Stearate USNF	0.75

Etodolac, Avicel PH 102, Starch 1500 and PVP K-30 were blended in a double cone blender. Aerosil 200, sifted through BSS #60, was added to the blend and mixed for 2 minutes. The blend was granulated with water and dried at 60°C for 4 hours. Dried material was sifted to obtain fraction of BSS #44/85 and lubricated with magnesium stearate (0.75g). The dried and lubricated granules (150.g) were sprayed with the prepared coating solution as described in Example 1 (Table 1.1). The total polymer coating of 12.0% by weight of the core was sufficient to mask the bitter taste of the drug. The total solids applied was 26%. The coated granules gave optimum dissolution as shown in Table 3.2.

Table 3.2

Time (Min.)	Percent drug released	
	Phosphate Buffer pH 7.5; 100rpm; 900ml	
	Uncoated	Coated
5	86.60	29.70
10	91.37	73.10
15	93.43	88.00
20	94.00	92.80
25	--	94.40
30	--	94.90

EXAMPLE 4

Table 4.1

Ingredient	Amount used (g)
Paracetamol USP	260.0
Microcrystalline Cellulose USNF (Avicel® PH 102)	88.0
Pregelatinized Starch USNF (Starch 1500)	10.0
Povidone USP (PVP K-30)	30.0
Colloidal Silicon Dioxide USNF (Aerosil® 200)	2.0
Magnesium Stearate upto	0.75

Paracetamol, Avicel PH 102, Starch 1500 and PVP K-30 were blended in double cone blender. Aerosil 200 was sifted through BSS #60 and blended for 2 minutes. The blend was granulated with water and dried at 60°C for 4-5 hours. 150 g of the dried fraction (BSS #44/85) was lubricated with magnesium stearate (0.75 g). The dried and lubricated granules (150g) were sprayed with the prepared coating solution as described in Example 1 (Table 1.1). The total polymer and solids applied were 8% and 17.5% by weight of the core, respectively which was sufficient to mask the taste of the drug without affecting the dissolution (Table 4.2).

Table 4.2

Time (Min.)	Percent drug released	
	Phosphate Buffer pH 5.8; 50rpm; 900ml	
	Uncoated	Coated
5	76.10	61.90
10	96.30	86.60
15	96.90	92.60
20	97.00	94.10
25	97.40	94.40
30	--	94.90

EXAMPLE 5

Table 5.1

Ingredient	Amount used (g)
Ciprofloxacin Hydrochloride USP (equivalent to 200g Ciprofloxacin USP)	239.0
Hydroxypropyl Cellulose USNF (HPC-L)	11.2
Colloidal silicon dioxide USNF (Aerosil® 200)	0.75

Microcrystalline cellulose USNF, (Celphere®)	100.0
Talc USP (Aqueous Talc Dispersion 30% w/w)	14.0
Purified Water USP upto	670.0

A dispersion was prepared by dissolving HPC-L in water, followed by the addition of ciprofloxacin hydrochloride and talc with vigorous stirring. The suspension was homogenised for 30 minutes, sieved and coated on 100 g microcrystalline cellulose spheres (Celphere® , FMC Corp., USA) having an average particle size of 170µm.

Procedure for layering : Celphere beads (100 g) were introduced into the processing chamber of Wurster coater (Glatt GPCG-1 from Glatt GmbH, Germany) and the prepared drug suspension was sprayed from the bottom at a spray rate of 5 - 9 g/min. After spraying was complete the drug loaded cores were dried.

150 g of the dried cores were lubricated with 0.75 g Aerosil® (sifted through BSS #60 mesh) and sprayed with the prepared coating solution described in Table 5.2, as follows:

Table 5.2

Ingredient	Amount used (g)	Dry wt. (g)
Eudragit L30D	66.67	20.0
Carbomer (Aqueous Carbopol® 971P Dispersion 1% w/w)	40.0	0.40
Polyethylene glycol USNF (PEG 1500)	3.06	3.06
Lactose Monohydrate USNF	2.04	2.04
Talc USP (Aqueous Talc Dispersion 40% w/w)	51.0	20.4
Purified Water USP upto	200.0	--

The total polymer content of the applied coat was 11.90% by weight of the core while the total solids application was 27% by weight of the core. The bitter taste of ciprofloxacin was masked with the applied coat without affecting dissolution, as shown in Table 5.3

Table 5.3

Time (Min.)	Percent drug released	
	0.1N HCl; 75 rpm; 900ml, USP app-2	
	Uncoated	Coated
5.0	87.0	7.20
10.0	97.8	27.2
15.0	100.7	46.3
20.0	-	62.90
25.0	-	76.0
30.0	-	85.1

EXAMPLE 6

Table 6.1 describes another coating composition containing a film forming polymer (ethyl cellulose) and a swellable polymer (carbopol).

Table 6.1

Ingredient	Amount used (g)	Dry wt. (g)
Ethyl Cellulose	100.0	30.0
Aqueous dispersion USNF (Aquacoat® ECD-30)		
Carbomer	60.0	0.60

(Aqueous Carbopol® 971P Dispersion 1% w/w)		
Triethyl Citrate USNF	6.0	--
Talc USP (Aqueous Talc Dispersion 30% w/w)	30.0	9.0
Purified Water USP upto	200.0	--

To prepare the coating solution an aqueous talc dispersion (30% w/w) was added to a 1% carbopol dispersion in water under stirring for 30 minutes. The carbopol – talc dispersion was finally added into plasticized (with triethyl citrate) ethyl cellulose dispersion with stirring for 30-40 minutes.

Core containing Paracetamol were prepared using the formula described in Table 6.2.

Table 6.2

Ingredient	Amount used (g)
Paracetamol USP	260.0
Povidone USP (PVP K-30)	28.0
Lactose Monohydrate USNF	18.0
Microcrystalline cellulose USNF (Avicel® PH 101)	90.0
Colloidal Silicon Dioxide USNF (Aerosil® 200)	4.0

Total	400.0
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Paracetamol, PVP K-30, Lactose, and Avicel PH 101 were mixed in a double cone blender for 10 minutes. They were then granulated with water, dried in a tray drier at 60°C for 4 hours and sifted to give BSS fraction #30/85. The granules thus obtained were lubricated with Aerosil 200 and sprayed with the prepared coating solution using Wurster Coater (Glatt GPCG-1, GmbH, Germany). The total polymer content of the coat applied was 12% by weight of the core. This coating effectively masked the pungent taste of paracetamol and also gave the desired dissolution profile as shown in Table 6.3

Table 6.3

Time (Min.)	Percent drug released	
	PH 5.8 Phosphate buffer; 50 rpm; 900ml	
	Uncoated	Coated
5.0	90.1	23.7
10.0	97.7	62.4
15.0	97.9	88.0
20.0	98.1	98.2
25.0	98.3	98.9
30.0	98.4	99.3

EXAMPLE 7

Example 7 deals with the same coating composition as given in Table 6.1, wherein ethyl cellulose has been combined with carbopol in a 100 : 2 proportion. The drug particles which have been coated is constituted of ciprofloxacin base and its composition is described in Table 7.1.

Table 7.1

Ingredient	Amount used (g)
Ciprofloxacin USP	50.0
Lactose Monohydrate USNF	3.5
Povidone USP (PVP K-30)	5.5
Microcrystalline cellulose USNF (Avicel PH101)	17.5
Colloidal Silicon Dioxide USNF (Aerosil 200)	00.75
Total	77.25

Weighed amount of ciprofloxacin, lactose, Avicel PH 101 and PVP K-30 were sifted through BSS #44 and dry mixed in a double cone blender. The blend was granulated with sufficient water to form a cohesive mass. The wet mass was dried in a tray drier and sifted through BSS #30 and retained on BSS #85. The dried material was lubricated with sifted Aerosil (sieved through BSS #60) and then loaded

in Glatt GPCG-1 Wurster for coating with ethyl cellulose-carbopol solution (described in Table 6.1).

A total polymer application of 15% of the weight of the cores (total solids applied were 34.35%) was sufficient to mask the bitter taste of ciprofloxacin without affecting the dissolution significantly.

Table 7.2 shows the dissolution profiles of the coated and uncoated granules using USP apparatus - 2 at 75 rpm in 900 ml of 0.1N hydrochloric acid.

Table 7.2

Time (Min.)	Percent drug released	
	0.1N HCl, 75 rpm; 900ml, USP app-II	
	Uncoated	Coated
5.0	83.3	12.8
10.0	97.7	31.7
15.0	97.8	58.7
20.0	98.1	70.8
25.0	-	82.6
30.0	-	95.2

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

WE CLAIM :

- 1 A coating composition, used for the film coating of pharmaceutical cores containing the drug, said composition comprising a suitable film forming material in combination with a high viscosity swellable polymer and optionally other suitable ingredients for coating including lubricants, plasticisers and channeling agents.
2. The composition of claim 1, wherein the film forming material comprises methacrylic acid copolymers, polymethacrylate-methylmethacrylate copolymers, alkyl celluloses or mixtures thereof.
3. The composition of claim 2, wherein the dry weight of the film forming polymer applied is upto a maximum of 30% of the weight of the core.
4. The composition of claim 1, wherein the high viscosity swellable polymer comprises carbopol, carragennan, polyvinyl alcohol, cellulosic polymers or other suitable high viscosity gums.
5. The composition of claim 4, wherein the swellable polymer is present from 0.1 to 20% w/w of the dry weight of film forming polymer.
6. The composition of claim 4, wherein high viscosity swellable polymer is carbopol.

7. The composition of claim 1, wherein channeling agents are included and are selected from the group consisting of lactose, starch, talc and mixtures thereof.
8. The composition of claim 7, wherein the channeling agent is present in an amount up to 100% of the dry weight of polymers.
9. The composition of claim 8, wherein the channeling agent is present in an amount up to 60% of the dry weight of polymers.
10. The composition of claim 9, wherein the channeling agent is present in an amount up to 30% of the dry weight of polymers.
11. The composition of claim 1, wherein the lubricants are present and are selected from the group consisting of talc, glyceryl monostearate, magnesium stearate, colloidal silica and mixtures thereof.
12. The composition of claim 11, wherein the lubricant is present in an amount up to 200% of the dry weight of the film forming polymer.
13. The composition of claim 12, wherein the lubricant is present in an amount up to 100% of the dry weight of the film forming polymer.
14. The composition of claim 1, wherein the plasticisers are incorporated in the film and are selected from the group consisting of polyethylene glycol, acetylated

monoglycerides, glyceryl monostearate, glyceryl triacetate, acetyl triethylcitrate, triethylcitrate, dibutyl phthalate, dibutyl sebacate and mixtures thereof.

15. The composition of claim 14, wherein the plasticizer is present in an amount upto 40% of the dry weight of film forming polymer.
16. The composition of claim 15, wherein the plasticizer is polyethylene glycol (PEG).
17. The composition of claim 1, which includes 0.5 to 30% of the dry weight of the polymers by weight of the cores.
18. The composition of claim 14, wherein the coated particles are formulated as sprinkles, dry powder, liquitabs, suspension, emulsion, or as whole, chewable, or dispersible tablet, or any other suitable oral dosage forms.

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(54) Title: **TASTE MASKING COATING COMPOSITIONS**

(57) Abstract: A coating composition is described for the film coating of pharmaceutical cores containing the drug, said composition comprising a suitable film forming material in combination with a high viscosity swellable polymer.



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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER IPC(7) : A61K 9/14 US CL : 424/489 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 424/489 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,958,459 A (CHASIN et al.) 28 September 1999, col. 4, lines 9-16 and 40-44; col. 5, lines 14-28 and 45-52; col. 6, lines 4-31 and 34-55; col. 7, lines 14-22; col. 8, lines 1-9 and 40-56; col. 10, lines 34-56; and col. 13, line 58.	1-18
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* "A" "B" "L" "O" "P"	Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance earlier document published on or after the international filing date document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) document referring to an oral disclosure, use, exhibition or other means document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application has aided to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention requires to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "a" document member of the same genus family
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Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230		Authorized officer: <i>William Benston</i> WILLIAM BENSTON Telephone No. (703) 308-1233

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